lines 10-11. (Indeed, an important aspect of the subject matter claimed herein is to use the aptamer technology of Griffin to achieve the quantitative measurement of low abundance molecules.) So Griffin does not come close to teaching the invention claimed herein.

In order to plug the major gap that exists in Griffin as a reference, the office action argues that Jayasena et al. "teach methods permitting quantification ... of a target", using aptamers. Office action, p. 6. But Jayasena does not plug the gap. Whereas Jayasena teaches only that quantification can be achieved using fluorescence, Col. 5, lines 36-40, various independent claims herein require "using a quantitative replicative procedure to determine a quantity of aptamer specific for each target molecule". A quantitative replicative procedure, as required by the claims, may be implemented by using a quantitative polymerase chain reaction. Application, for example, at p. 5, lines 22-23. Jayasena's procedure for quantification is nothing of this kind—it does not use a quantitative replicative procedure— but instead requires "simply comparing the fluorescence measurement with that obtained from a control." Col. 5, lines 36-40.

So Jayasena adds nothing to Griffin. In fact a careful study of Jayasena shows that it teaches away from the subject invention. In order to quantify aptamer that is bound to the target, Jayasena teaches that it is necessary to employ, in addition to the original target-specific aptamer, a second nucleic acid ligand, which is termed a "ligand beacon". Col.5, lines 16-31; and for example, col. 10, line 52 to col. 11, line 6 and passim. According to the embodiment of Fig. 2 of this reference, in the presence of the ligand beacon, the target-specific aptamer will fluoresce but only if the target-specific aptamer is not bound to the target. Fig. 2; Col. 6, lines 6-10, and col. 14, line 28 through col. 16, line 12; and col. 5, lines 8-40. The aptamer-ligand beacon combination of Fig. 2 results only from aptamer that is *not* bound to the target. *Id.* Although this reference suggests another embodiment in which the ligand beacon binds selectively to the target-specific apatmer when the latter aptamer is bound to the target (col. 10, line 65 to col. 11, line 6; col. 14, lines 29-31), still the measurement depends on a second mechanism that is independent of the binding of the target-specific aptamer to its target. In other words, Jaysena teaches that quantification of target-specific aptamer that is bound to the target should be accomplished by measuring a binding phenomenon that is wholly distinct from the

aptamer-target combination—namely the aptamer-ligand beacon combination that produces the fluorescence.

Of course, the quantitative replicative procedure required by the claims herein looks directly at the aptamer that *is* bound to the target, and not (as Jayasena does) to unbound aptamer. Indeed, claim 1 requires, in element (c), separating the unbound aptamer, and the quantitative replicative procedure of element (d) is used on the second sample containing bound aptamer only when the unbound aptamer has been separated.

In sum, Jayasena uses an approach that is completely different from that which is claimed herein. Not only is there no disclosure in Jayasena of the subject matter herein, but also the reference teaches away from the subject matter claimed herein.

The rejection under 35 U.S.C. § 112

The office action expresses concern that a person of ordinary skill in the art would not understand what is meant by the use of the term "substantially all" in claim 1. However, a person of ordinary skill in the art is one who would understand and have access to the concepts that are set forth in the art cited by the Examiner in rejecting the claims—art that includes Griffin and Jayesena—and which is undisputedly enabling for the subject matter disclosed, given that these references were asserted as a basis for rejection under 35 U.S.C. § 103. *Seymour v. Osbourn*, 78 U.S. 516, 555 (1870); *Preemption devices, Inc. v. Minnesota Mining and Manufacturing Co.*, 732 F.2d 903, 906 (Fed. Cir. 1984). Such a person therefore knows how to design high-affinity aptamer specific to a target. Griffin and Jayesena both specifically describe the SELEX process in detail, which enables the selection of high-affinity aptamer for a specified target. E.g. Jayesena, col. 11, line 50 through col. 13, line 45. See additionally PCT WO 99-07724. referred to in the application on p. 2, lines 3-8, and incorporated by reference therein, reference AE as submitted herein, p. 1, line 31 to p. 5, line 28. Binding phenomena are, and are well known in the art to be, equilibrium processes. The power of the SELEX method is the ability to select and enrich for aptamers to a desired target that have unprecedented specificity and therefore high-affinity binding to the desired target. *Id.* and Griffin defines "specifically binding oligonucleotides" or "aptamers" as "oligonucleotides ... forming complexes with an intended target molecule in an environment wherein other substances in the same environment are not complexed". Col.

15, lines 26-41 (containing full discussion of binding constants, and reciting Kd values that are "2-fold, preferably 5-fold, more preferably 10-fold less than Kd with respect to target and the unrelated material or accompanying material in the environment. Even more preferably the Kd will be 50-fold less, more preferably 100-fold less, and more preferably 200-fold less." (See also more generally, col. 15, line 26 through col. 16, line 32, discussion aptamer selection, binding, and specificity.) Therefore a person of ordinary skill in the art would understand that the aptamer used in the claimed invention should be selected to have a Kd of at least 2-fold less than the "Kd with respect to target and the unrelated material or accompanying material in the environment" .

It is therefore certain that a person of ordinary skill in the field of the subject matter claimed herein can implement the target-specific aptamer selection and subsequent enrichment to provide high affinity aptamer with any desired low Kd value (at least 2-fold) to provide any desired level of discrimination. Such a person also knows, by reading claim 1 and the application, that the aptamer that is bound to the target is what is measured using a quantitative replicative procedure. The measurement of bound aptamer thus determines the measurement of the target molecule. This is the context in which "substantially all" can be understood by a person of ordinary skill in the art.

Given (i) that the person of ordinary skill in the art knows how to select aptamer that binds to the target with high affinity and any desired Kd value, and (ii) that such a person also knows that the high-affinity aptamer thus selected binds to the target and determines the measurement, it is plainly known to a person of ordinary skill in the art to design a system having any desired degree of accuracy . Such a person understands "substantially all" of the target molecules being bound to aptamer in the context of the determination of element (d) as aptamer selected to have a Kd value providing the desired degree of accuracy.

In other words, when one looks to the application in view of the prior art of record, the context is perfectly clear to a person of ordinary skill in the art what is meant here by "substantially all".

Other matters

In response to the office action, the abstract has been amended. Accompanying this response is an Information Disclosure Statement providing the reference identified in

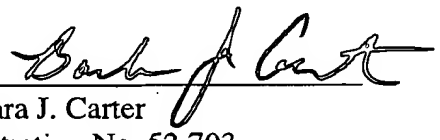
the application. Such a reference is believed to be pertinent primarily as background material.

Conclusion

Applicants herein petition for a two-month extension of time. Please charge account No. 19-4972 $205 to cover the fee for the two-month extension. In addition, please charge account number 19-4972 $180 to cover the fee for submission of an Information Disclosure Statement after the first office action but before final action or allowance. It is believed that no additional extension of time is needed; however, this conditional petition for an additional extension of time is being made in the event that the need for an additional extension has been overlooked. If any additional fees are required for the timely consideration of this application, please charge deposit account number 19-4972.

It is submitted that all of the claim rejections have been addressed and that all of the pending claims are now in a condition for allowance. Accordingly, Applicants respectfully request reconsideration of the application and issuance of a notice of allowance. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

Respectfully submitted,



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